

**UNITED STATES DISTRICT COURT  
FOR THE NORTHERN DISTRICT OF OHIO  
EASTERN DIVISION**

**IN RE NATIONAL PRESCRIPTION  
OPIATE LITIGATION**

**This document relates to:**

*Track Three Cases*

**MDL No. 2804  
Case No. 17-md-2804  
Judge Dan Aaron Polster**

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**DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY  
DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS  
AND TESTIMONY OF DR. KATHERINE KEYES**

**EXHIBIT 14**

## Original Investigation

# Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts

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**IMPORTANCE** Pharmaceutical industry payments to physicians may affect prescribing practices and increase costs if more expensive medications are prescribed.

**OBJECTIVE** Determine the association between industry payments to physicians and the prescribing of brand-name as compared with generic statins for lowering cholesterol.

**DESIGN, SETTING, AND PARTICIPANTS** Cross-sectional linkage of the Part D Medicare prescriptions claims data with the Massachusetts physicians payment database including all licensed Massachusetts physicians who wrote prescriptions for statins paid for under the Medicare drug benefit in 2011.

**MAIN OUTCOMES AND MEASURES** The exposure variable was a physician's industry payments as listed in the Massachusetts database. The outcome was the physician's rate of prescribing brand-name statins. We used linear regression to analyze the association between the intensity of physicians' industry relationships (as measured by total payments) and their prescribing practices, as well as the effects of specific types of payments.

**RESULTS** Among the 2444 Massachusetts physicians in the Medicare prescribing database in 2011, 899 (36.8%) received industry payments. The most frequent payment was for company-sponsored meals ( $n = 639$  [71.1%]). Statins accounted for 1 559 003 prescription claims; 356 807 (22.8%) were for brand-name drugs. For physicians with no industry payments listed, the median brand-name statin prescribing rate was 17.8% (95% CI, 17.2%-18.4%). For every \$1000 in total payments received, the brand-name statin prescribing rate increased by 0.1% (95% CI, 0.06%-0.13%;  $P < .001$ ). Payments for educational training were associated with a 4.8% increase in the rate of brand-name prescribing ( $P = .004$ ); other forms of payments were not.

**CONCLUSIONS AND RELEVANCE** Industry payments to physicians are associated with higher rates of prescribing brand-name statins. As the United States seeks to rein in the costs of prescription drugs and make them less expensive for patients, our findings are concerning.

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In the United States, many physicians have financial relationships with pharmaceutical manufacturers.<sup>1-3</sup> These relationships include the receipt of industry-sponsored meals, subsidies for continuing medical education, fees for consulting and participation on speaking bureaus, grants, and payments for education and training. Payments by pharmaceutical manufacturers to physicians outside the research context may be problematic, because they can be perceived as conflicts of interest that could interfere with physicians' responsibilities to their patients.

Concerns about the financial relationships between physicians and the pharmaceutical industry have led to calls for transparency, as well as increased regulation.<sup>4</sup> Some states,

such as Massachusetts, Vermont, Minnesota, and West Virginia, have implemented programs that require physicians to disclose their financial relationships with pharmaceutical manufacturers.<sup>5-7</sup> Most recently, the Affordable Care Act established the federal Open Payments database, which in late 2013 started collecting pharmaceutical manufacturer payments to physicians and publicly posting them.<sup>8</sup>

The regulation of physicians' financial relationships with industry and the importance of transparency about these relationships are controversial.<sup>9-14</sup> A key concern about industry payments to physicians is the potential for increased prescribing of brand-name drugs instead of lower-cost generic drugs that are equally safe and effective or non-drug-based

therapies. Some evidence suggests that the financial relationships between industry and physicians may lead to substandard prescribing practices,<sup>15-19</sup> but some physicians and policymakers remain unconvinced.<sup>20,21</sup> One reason is that previous studies<sup>15,16,18,19</sup> have used small samples or self-reports in surveys. Data are now available from large physician payment databases; studies using such databases may provide further insight.<sup>22</sup> For example, Massachusetts requires pharmaceutical companies to collect and report to the state payments of more than \$50 to physicians.<sup>23</sup> Using Massachusetts' data on physician payments and federal data on prescriptions for Medicare beneficiaries, we evaluated the association between industry payments to physicians and the prescribing of brand-name statins.

## Methods

### Data Sources

This cross-sectional study was approved by the Brigham and Women's Hospital internal review board committee. It involved 2 large databases containing data for January 1 to December 31, 2011. The first was Medicare Part D prescription claims data prepared by the Centers for Medicare and Medicaid Services (CMS). These data were made publicly available after a Freedom of Information Act request by the news organization ProPublica.<sup>24</sup> This database includes all physicians who had at least 50 prescription drug claims (including refills) covered by Medicare Part D. To protect patient privacy, we did not include physicians who prescribed drugs to 10 or fewer Medicare beneficiaries during 2011. The claims database included the prescribing physician's name, National Prescriber Identification (NPI) number, and practice address. ProPublica assigned each medication, including brand-name and generic identity, a drug identification number. Claims counts including refills were available for each of the drugs, with generic and brand-name versions reported separately. A specific prescription associated with a particular physician was included in the database only if there were 50 or more claims for that drug associated with that physician. For example, if a physician prescribed drug X 60 times (including refills) but drug Y 40 times, only the drug X prescription claims would be associated with that physician's information. Thus, any statins for which there were fewer than 50 claims were not counted in the physician's brand-name percentage calculation. The Medicare Part D data set reflected only prescriptions that were filled. Data was analysed in March of 2015.

The second data source was the Massachusetts physician open payment database, compiled by the Massachusetts Department of Health.<sup>23</sup> Derived from pharmaceutical manufacturer reports, this database included payment information of \$50 or more in value to physicians during the study period. The database aggregates the payment types to each physician into 8 categories (defined in the state law): food, grants or educational gifts, bona fide services, educational training (payments received by covered recipients in conjunction with education and training), continuing medical education, charitable donations, marketing studies, and other. The

### Key Points

**Question** What is the association between pharmaceutical industry payments to physicians and their prescribing of brand-name statins to lower cholesterol instead of less expensive but equally effective generics?

**Findings** This cross-sectional study used 2011 data from a Massachusetts database of industry payments to physicians and a Medicare prescribing database, and found that physicians with no industry payments had a median prescribing rate for brand-name statins of 17.8%. For every \$1000 in industry payments received, this prescribing rate increased by 0.1%.

**Meaning** Industry payments to physicians were associated with higher rates of prescribing brand-name statins.

database included identifiable physician information including name, NPI number, and practice address. Using these common identifiers, we linked the 2 databases.

### Statin Prescription Drug Claims

We focused on statins for 2 reasons. First, these drugs are prescribed frequently. Second, although some statins are available as generics, others are brand-name only and extensively promoted by their manufacturers. We included these statins or statin-containing products: niacin, extended-release and lovastatin (Advicor); lovastatin, extended-release (Altoprev); amlodipine-atorvastatin (Caduet); rosuvastatin (Crestor); sitagliptin-simvastatin (Juvisync); fluvastatin (Lescol); fluvastatin, extended-release (Lescol XL); atorvastatin (Lipitor); ezetimibe-atorvastatin (Liptruzet); pitavastatin (Livalo); lovastatin (Mevacor); pravastatin (Pravachol); niacin, extended-release and simvastatin (Simcor); ezetimibe-simvastatin (Vytorin); and simvastatin (Zocor). During the study period, rosuvastatin and atorvastatin were available as brand-name only except for the last month of 2011, when a generic version of atorvastatin became available.

### Statistical Analysis

The exposure variable was a physician's financial payments from pharmaceutical companies as listed in the Massachusetts payment database. The outcome was the physician's rates of prescribing brand-name statins. The brand-name prescribing rate was calculated as the percentage of all brand-name statins claim counts divided by the total claims counts for all brand-name and generic statins. A claim is the physician's prescription filled by the pharmacy, which is then submitted to and paid by the insurer. We used linear regression models to analyze the association between the intensity of physician-industry relationships (as determined by the amount of industry payments) and prescribing of brand-name statins. We performed sensitivity analyses to check for nonlinearity of this relationship by including a squared term of payments received in the model and by reestimating the linear model using various cut-offs of total payments received. Adding a squared term for payments to the model allows for the possibility of a curvilinear relationship between payment and prescribing. A large coefficient on the squared term may be evidence of nonlinearity.

**Table 1. Characteristics of Industry Payments to Physicians in Massachusetts With Statin Prescriptions in the Medicare Database, 2011**

Categories of Payment Defined by Massachusetts Law <sup>2,3</sup>	Type of Industry Payment, No. (% Total) <sup>a</sup>
Food	639 (71.1)
Grants/education gifts	458 (50.9)
Bona fide services <sup>b</sup>	236 (26.3)
Educational training <sup>c</sup>	95 (10.6)
Other <sup>d</sup>	32 (3.6)
CME	3 (0.3)
Marketing studies <sup>e</sup>	NA
Charitable donations	NA

Abbreviations: CME, continuing medical education; NA, not applicable.

<sup>a</sup> Total n = 899, from a total of 2444 physicians with associated statin prescriptions covered by Medicare in our study sample.

<sup>b</sup> An arrangement for services including, but not limited to, research, participation on advisory boards, collaboration with 501(c)(3) organizations dedicated to the promotion of health and the prevention of disease, and presentations at pharmaceutical or medical device manufacturing company-sponsored medical education and training.

<sup>c</sup> Payments received by covered recipients in conjunction with education and training.

<sup>d</sup> Includes other nonexempt payments greater than \$50 in value not classified in the other categories of payment.

<sup>e</sup> Payments in conjunction with research other than genuine research.

We sought to determine whether specific types of industry payments to physicians were associated with their preferences for prescribing either brand-name or generic statins. We used a linear regression model that included binary indicators of receiving each payment type to determine the relationship between the types of physician-industry relationships and the extent of physicians' brand-name prescribing. We examined the most prevalent types of industry relationships in the Massachusetts database: food, bona fide services, grants, and educational training.

## Results

From 363 653 physicians in the Medicare Part D prescription claims database, we identified 9628 with a business address in Massachusetts, of whom 2444 had associated statin prescriptions covered by Medicare. More than one-third of these physicians (n=899 [36.8%]) had financial relationships with pharmaceutical manufacturers disclosed in 2011 (Table 1). The most frequent payment was for company-sponsored meals (71.1%), followed by grants (50.9%), bona fide services, (26.3%), and educational training (10.6%). The median total financial payment was \$260 (interquartile range [IQR], \$100-\$1188). Median value of payments attributed to meals was \$187 (IQR, \$87-\$403); to grants \$100 (IQR, \$67-\$160); to consulting and speaking bureaus \$3001 (IQR, \$579-\$11 750); and to educational training, \$345 (IQR, \$99-\$1015).

### Distribution of Claims for Brand-name and Generic Statins

Brand-name and generic statins accounted for 1559 003 prescription claims, with 22.8% (n = 356 087) for brand-

**Table 2. Claims for Brand-name and Generic Statins in 2011<sup>a</sup>**

Type of Drug	Claims, No.
Brand-name drug	
Lipitor	268 630
Crestor	84 380
Lescol	1368
Vytorin	881
Lescol XL	743
Caduet	85
Total brand-name	356 087
Generic drug	
Simvastatin	1 028 325
Pravastatin	115 910
Lovastatin	59 339
Atorvastatin	242
Total generic	1 203 816

<sup>a</sup> Claims include original fills and refills. Total brand-name and generic claims = 1559 903.

name drugs (Table 2). Atorvastatin (n = 268 630) accounted for 75.4% of the dispensed brand-name-only drugs. Simvastatin (n = 1 028 325) was the most frequently prescribed generic statin, accounting for 85.4% of the dispensed drugs available as generics.

### Financial Relationships and Brand-name Statin Prescribing

Physicians in the CMS database with eligible statin claims but who were not listed in the Massachusetts open payment database as receiving industry payments had a mean brand-name statin prescribing rate of 17.8% (95% CI, 17.2%-18.4%), which was about the same as the comparable rate for all physicians listed in the Massachusetts database 17.8% (95% CI, 17.3%-18.3%). Among physicians with industry payments reported in the Massachusetts database, every \$1000 in total payments received was associated with a 0.1% increase in the rate of brand-name statin drug prescribing (95% CI, 0.06%-0.13%;  $P < .001$ ) (Figure 1A). The overall relationship was linear, as demonstrated by the sensitivity analysis that included a squared term for total payments (Figure 1B). The small proportion of physicians with higher payments primarily drove the linear relationship. When the analysis was restricted to physicians with total payments of \$2000 or less, a linear relationship was no longer found (Figure 2).

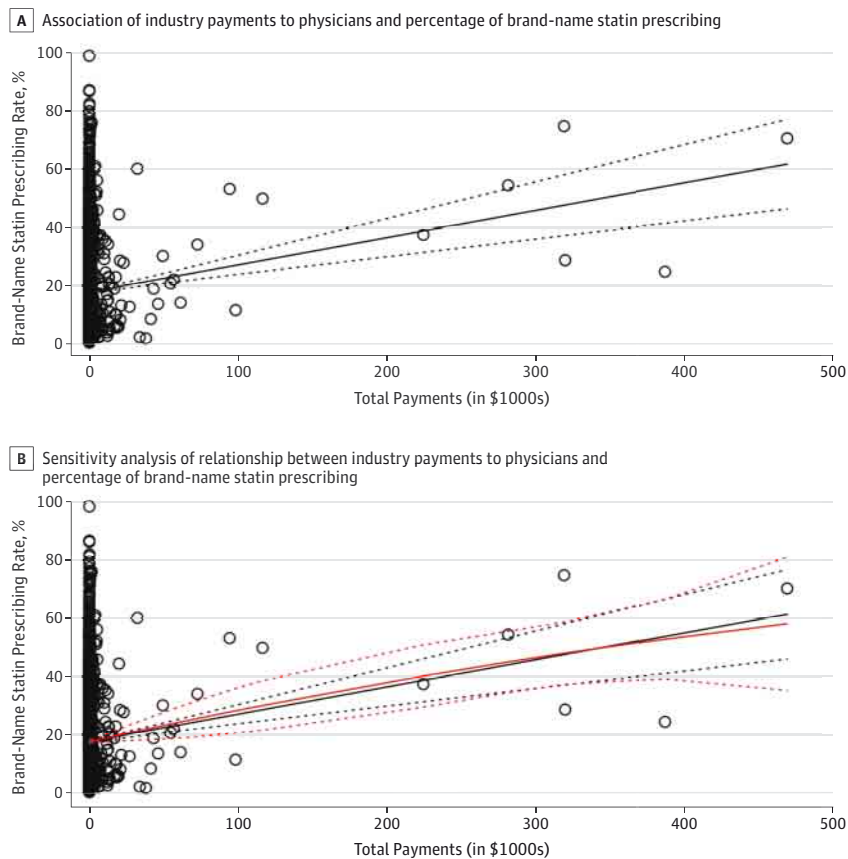
### Types of Payments and Brand-name Prescribing

Among physicians who received industry payments, payments for educational training were associated with an average 4.8% increase in brand-name prescribing compared with no receipt of educational training (95% CI, 1.55-7.95;  $P = .004$ ), but the other payment types such as food, consulting and speaking bureau, and grants were not (Table 3).

## Discussion

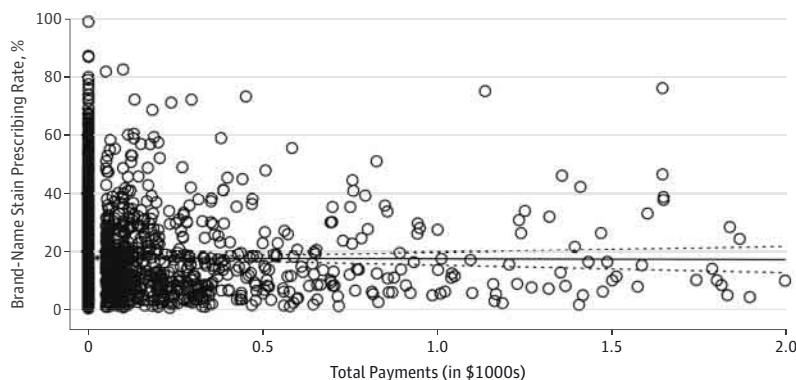
We found an association between industry payments to physicians and the prescribing of brand-name statins, a

Figure 1. Effect of Industry Payments on Brand-name Statin Prescribing



Each circle represents one physician. The solid black line is the estimated linear association between payment and brand name statin prescribing percentage and the dashed lines represent the 95% confidence bounds around the estimated associations. A, Association of industry payments to physicians and percentage of brand-name statin prescribing. B, Sensitivity analysis of relationship between industry payments to physicians and percentage of brand-name statin prescribing using squared terms. The solid orange line is the estimated association when including both linear and squared terms in the model.

Figure 2. Association of Financial Payments and Brand-name Statin Prescribing Among Physicians Receiving \$2000 or Less in Total Payment



Each circle represents one physician. The solid black line is the estimated linear association between payment and brand name statin prescribing percentage and the dashed lines represent the 95% confidence bounds around the estimated associations.

frequently prescribed class of medications with many low-cost generic options with similar effectiveness. For most patients diagnosed as having hypercholesterolemia, statins are interchangeable. Given the large cost differences between generic and brand-name statins (2- to 4-fold higher average wholesale price for brand-name statins) the financial effects on patients and the health care system are likely to be substantial. A recent study showed that initiation of generic stat-

ins was associated with improved cardiovascular outcomes among patients owing to better patient adherence.<sup>25</sup>

We also found a threshold effect in the association between industry payments to physicians and brand-name prescribing; when the analysis was limited to physicians who received \$2000 or less in total payments in 2011 the association was no longer significant. This result is consistent with the presumption that larger industry payments to physicians



**Table 3. Financial Payment Types and Their Association With Brand-name Prescribing Rates for Statins**

Variable	Increase in Brand-Name Prescribing, % (95% CI)	P Value
Food	-1.1 (-2.56 to 0.42)	.16
Bona fide services	-0.6 (-2.79 to 1.60)	.59
Grants/educational gifts	0.6 (-0.99 to 2.28)	.44
Educational training	4.8 (1.55 to 7.97)	.004

are more likely to influence physicians' prescribing behavior. In addition, our findings were likely diluted because we included all industry payments, not just those from manufacturers of statins or directed to statin-relevant activities. Thus, it is possible that the effect on prescribing that we found is stronger among physicians with close ties to particular companies.

Open payment databases, such as the one in Massachusetts, promote transparency with respect to industry payments that can potentially bias physician behavior. Our analysis suggests that certain payment types may be more of a cause for concern than others. Of the various forms of payments received by physicians, those for educational training support were associated with higher rates of brand-name prescribing. Some have argued that such payments are essentially marketing payments and should be disclosed or banned. Since the public release of the Open Payments database in 2014, pharmaceutical companies no longer have to report to Massachusetts the payments that were disclosed to the federal government, unless required reporting by Massachusetts was not covered by Open Payments. Despite the promise of state and federal payment databases and their intent to promote transparency, it is not yet known how widely such databases are being used by patients or whether physician prescribing behaviors have changed.

Our cross-sectional study has notable limitations. We could detect an association only between brand-name prescribing and financial relationships. It is possible that the physicians who more frequently prescribed brand-name pharmaceuticals were also those who were more open to receiving industry funding for meals, conferences, or other purposes. Alternatively, high prescribers of brand-name

drugs may have been sought after by pharmaceutical companies to promote their products through various marketing activities, such as participation in speakers' bureaus. Manufacturers purchase prescribing data for individual physicians from IMS Health and other vendors and use such information to guide their marketing efforts. Because the Medicare Part D prescription database includes only insurance claims for prescriptions that were filled, our analysis may have underestimated the extent of brand-name prescribing. Research suggests that prescriptions for brand-name prescriptions are less likely to be filled than prescriptions for generics, owing to their higher cost.<sup>26,27</sup>

Our findings are also limited by the accuracy of reporting of industry payments in the Massachusetts; there is no process to ensure the completeness and accuracy of reports. For example, companies may choose to report certain payments to physicians as bona fide services, a catch-all payment category that might cover payments for marketing-related consulting, participating in speakers bureaus, and research. In addition, payments for education might be reported under several payment categories, such as grants/educational gifts, and educational training. We were unable to determine the frequency of misattribution of the payment category or underreporting of payments. Nor were we able to control for certain physician characteristics not found in either database (eg, practice characteristics, level of experience) that may have an impact on prescribing patterns. We could not determine which physicians received payments from a specific company and analyze their prescribing of that company's products.

## Conclusions

As the United States seeks to rein in the costs of prescription drugs and make them less expensive for patients, our findings are a cause for concern. We found that pharmaceutical industry payments to physicians were associated with higher rates of prescribing brand-name statins. On average, a \$1000 increase in total payments was associated with a 0.1% increase in the percentage of brand-name prescriptions.

### ARTICLE INFORMATION

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**Author Contributions:** Dr Yeh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Yeh, Kesselheim.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Yeh.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Yeh, Franklin, Avorn, Landon.

**Obtained funding:** Avorn, Kesselheim.

**Administrative, technical, or material support:** Yeh, Avorn.

**Study supervision:** Franklin, Avorn, Kesselheim.

**Conflict of Interest Disclosures:** None reported.

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